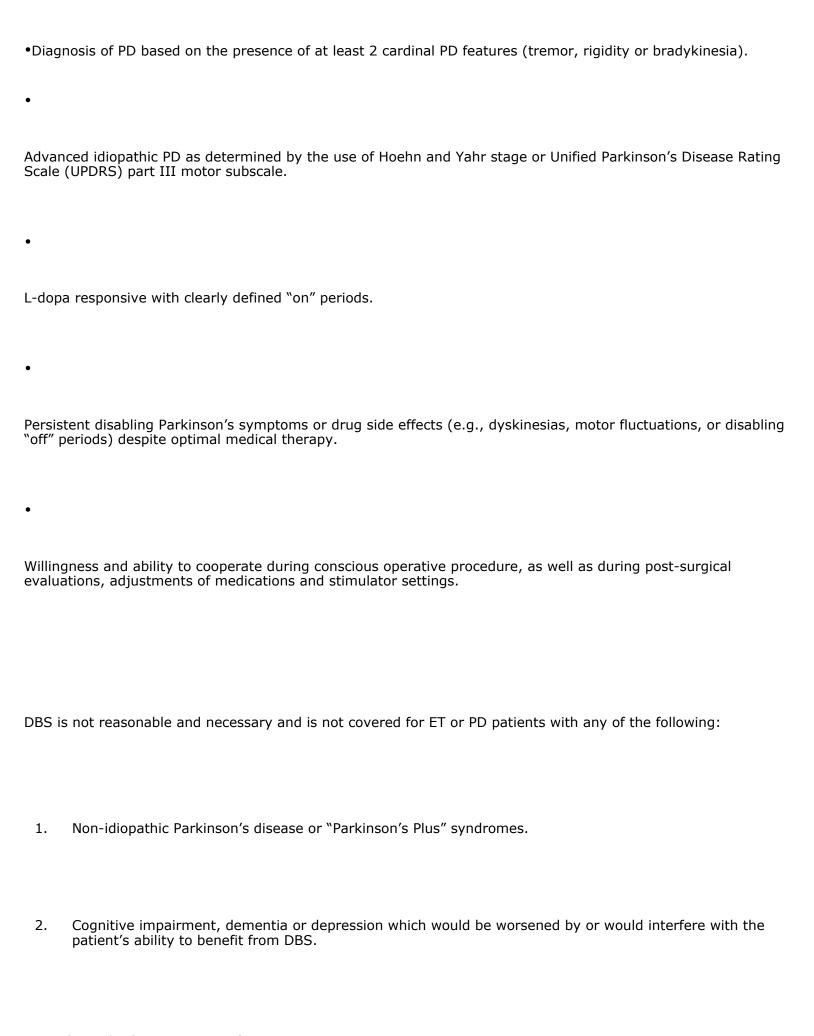
# Decision Memo for Deep Brain Stimulation for Parkinson's Disease (CAG-00124N)

# **Decision Summary**

Effecti thalam bilater	ve upon implementation of our national coverage determination, Medicare will cover <i>unilateral or bilateral nic VIM DBS</i> for the treatment of essential tremor (ET) and/or Parkinsonian tremor and <i>unilateral or al STN or GPi DBS</i> for the treatment of Parkinson's disease only under the following conditions:
1.	Medicare will only consider DBS devices to be reasonable and necessary if they are Food and Drug Administration (FDA) approved devices for DBS or devices used in accordance with FDA approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials.
2.	For thalamic VIM DBS to be considered reasonable and necessary, patients must meet all of the following criteria:
3.	Diagnosis of essential tremor (ET) based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidit or bradykinesia)) which is of a tremor- dominant form
4.	Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.
5.	Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.

•For STN or GPi DBS to be considered reasonable and necessary, patients must meet all of the following criteria:

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3.	Current psychosis, alcohol abuse or other drug abuse.
4.	Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.
5.	Previous movement disorder surgery within the affected basal ganglion.
6.	Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation
shortw	ts who undergo DBS implantation should not be exposed to diathermy (deep heat treatment including vave diathermy, microwave diathermy and ultrasound diathermy) or any type of MRI which may adversely the DBS system or adversely affect the brain around the implanted electrodes.
	hould be performed with extreme caution in patients with cardiac pacemakers or other electronically lled implants which may adversely affect or be affected by the DBS system.
	SS lead implantation to be considered reasonable and necessary, providers and facilities must meet all of lowing criteria:
1.	Neurosurgeons must: (a) be properly trained in the procedure; (b) have experience with the surgical management of movement disorders, including DBS therapy; and (c) have experience performing stereotactic neurosurgical procedures.

2.	Operative teams must have training and experience with DBS systems, including knowledge of anatomical and neurophysiological characteristics for localizing the targeted nucleus, surgical and/or implantation techniques for the DBS system, and operational and functional characteristics of the device.				
3.	Physicians specializing in movement disorders must be involved in both patient selection and post-procedure care.				
4.	Hospital medical centers must have: (a) brain imaging equipment (MRI and/or CT) for pre-operative stereotactic localization and targeting of the surgical site(s); (b) operating rooms with all necessary equipment for stereotactic surgery; and (c) support services necessary for care of patients undergoing this procedure and any potential complications arising intraoperatively or postoperatively.				
the ap clinical best m	ong-term safety, effectiveness and optimal targeting for DBS have not been established, CMS will review propriateness of Medicare coverage as pertinent new evidence becomes available. This review will include follow-up and targeting information from the ongoing, randomized VA/NINDS Cooperative Trial comparing edical therapy with DBS of the STN and GPi for PD, as well as longer term clinical results from mandatory progress reports and final report to the FDA of Medtronic's bilateral DBS PMA postapproval study.				
Back to	<u>о Тор</u>				
De	cision Memo				
This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.					
TO:	Administrative File CAG: #00124N Deep Brain Stimulation (DBS) for Parkinson's Disease				

FROM: Steve Phurrough, MD, MPA

Director, Division of Medical and Surgical Services

Coverage and Analysis Group

Michelle Atkinson Liaison, Division of Operations and Committee Management Coverage and Analysis Group

Perry Bridger, MHS Policy Analyst, Division of Medical and Surgical Services Coverage and Analysis Group

Tanisha Carino, PhD Policy Analyst, Division of Operations and Committee Management Coverage and Analysis Group

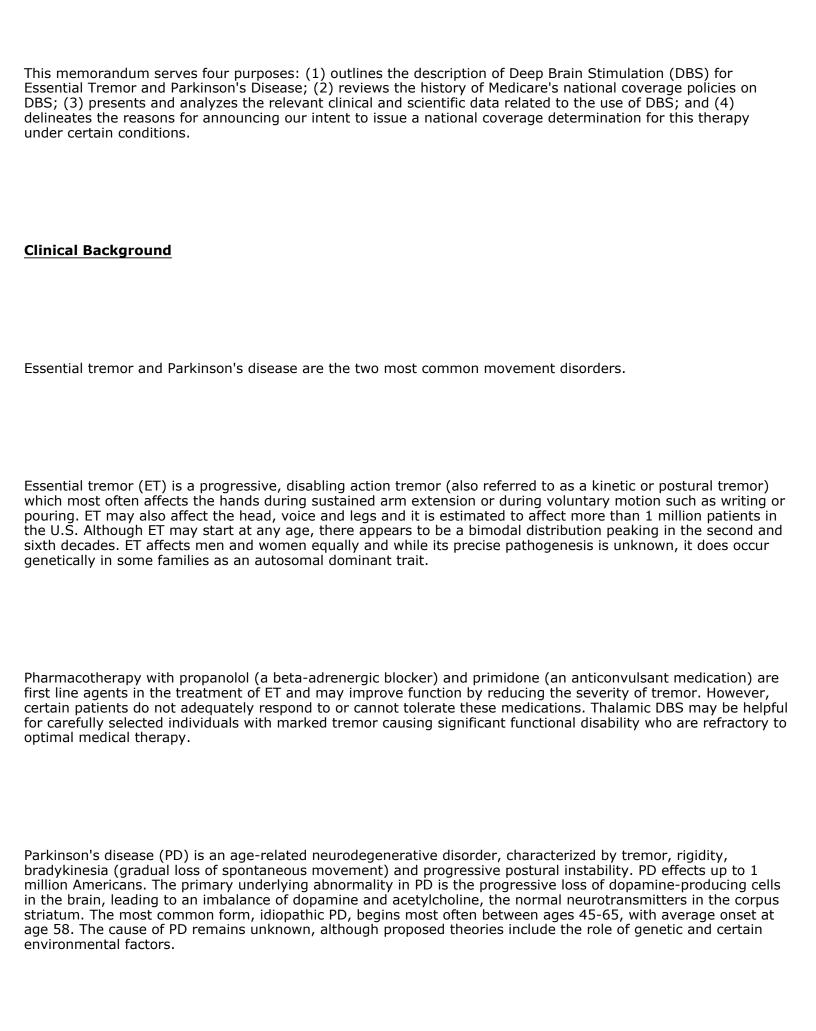
William Larson Health Insurance Specialist, Division of Medical and Surgical Services Coverage and Analysis Group

Lawrence Schott, MD, MS Medical Officer, Division of Medical and Surgical Services Coverage and Analysis Group

SUBJECT: National Coverage Determination Memorandum for Deep Brain Stimulation for

Essential Tremor and Parkinson's Disease

DATE: February 6, 2003



Treatments for PD include those which alleviate symptoms (symptomatic therapy), slow the loss of nerve cells (neuroprotective), and increase and/or improve cell function (restorative). Currently, symptomatic therapy - with medications, lesioning surgery or DBS - is the only available treatment for patients with PD. While neuroprotective and restorative therapies are in various stages of development, neuroprotection has yet to be demonstrated by any currently used therapeutic agent. Restorative therapy with fetal tissue implants or other grafts remains experimental. 1

Dopamine itself is ineffective for treatment because it is unable to cross the blood-brain barrier. Levodopa (L-dopa), which can cross the blood-brain barrier, is dopamine's immediate metabolic precursor and is converted to dopamine in the brain. L-dopa is the oldest and most potent symptomatic drug treatment and remains the gold standard for relieving the symptoms of PD. However, significant side effects may occur and include dyskinesias, motor fluctuations, and disabling periods of rigidity.

In practice, L-dopa is often administered in combination with carbidopa (Sinemet) to prevent the metabolism of L -dopa in the peripheral tissues, thereby reducing the dose of L-dopa and reducing side effects. Dopamine agonists (such as bromocriptine, pergolide, pramipexole and ropinirole), which directly stimulate dopamine receptors but are not as effective as L-dopa, are also used as an initial form of therapy in order to delay the need for L-dopa and its associated long-term adverse effects.

After 5 to 10 years of drug therapy it is often increasingly difficult to balance the control of PD symptoms with the adverse effects of these dopaminergic medications. For patients who become unresponsive to pharmacological treatments and/or have intolerable drug side effects, lesioning surgeries and DBS may be helpful for carefully selected patients. Lesioning surgeries, including thalamotomy and pallidotomy, have been treatments for Parkinson's disease for over 40 years and are based on precise localization and reduction of overactivity in the target nuclei of the brain. The creation of a small ablative lesion in the thalamus (thalamotomy) or in the globus pallidus interna (pallidotomy) involves neurosurgical insertion of an electrode into the thalamus or globus pallidus interna (GPi), heating of the tip of the electrode to result in a small area of necrosis in the target nucleus and subsequent removal of the electrode. Thalamotomy has been shown to be substantially effective for tremors, while pallidotomy potentially alleviates other symptoms of PD. Associated morbidities with these procedures, which include speech disturbances, dysequilibrium and cognitive dysfunction, severely limit their applicability. This is particularly the case for patients with bilateral symptoms.

DBS requires the stereotactic placement of an indwelling electrode in the brain. This treatment for PD is supported by observations that high-frequency stimulation of the affected neurons induces functional inhibition in target regions of the brain. DBS thus simulates the effect of a ablative surgical lesion but, unlike lesioning surgery DBS can be adjusted (or turned off) and the implanted electrode can be re-positioned (or removed). The mechanism of action remains unknown. Possible mechanisms include release of local inhibitory neurotransmitters, depolarization blockade, or jamming of abnormal neuron firing patterns.

The device currently used for DBS is the Activa® system developed by Medtronic, Inc. (Minneapolis, MN). The
system consists of several implantable and nonimplantable components (listed below), including a quadripolar
electrode (four contact sites arranged along the distal edge) which is stereotactically implanted into the targeted
structure. Stimulation parameters, including electrode contact site selection, stimulation pulse amplitude,
frequency, and width are then adjusted to optimize symptom relief.

#### Implantable components:

- Neurostimulator (a small, sealed device implanted beneath the skin in the chest);
- DBS™ Lead (a thin, insulated wire with 4 electrodes at the tip, implanted in the brain);
- Lead extension (a thin, insulated wire implanted under the skin of the head and neck, connecting the lead to the neurostimulator)

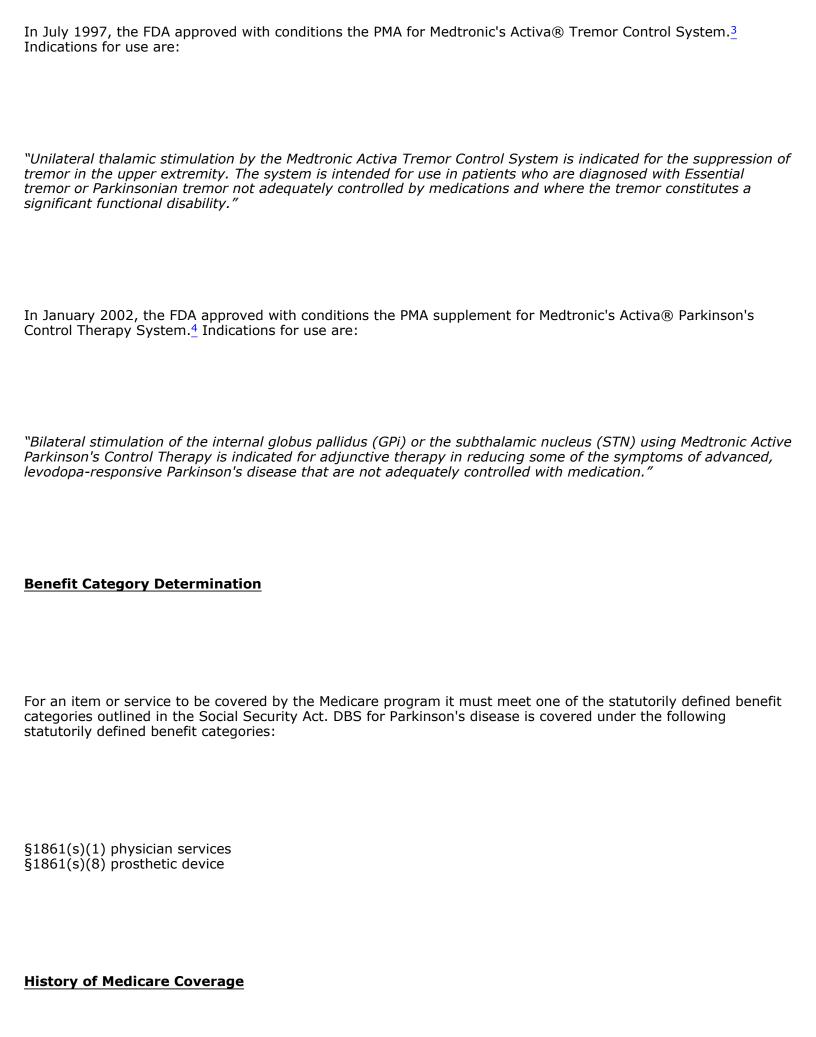
### Nonimplantable components:

- Physician Programmer with MemoryMod software cartridge (to allow the system to be noninvasively adjusted);
- Handheld patient therapy controller

The overall DBS procedure consists of the following basic segments:

- Stereotactic image acquisition and coordinate calculation, using computed tomography (CT) or magnetic resonance imaging (MRI);
- Under local anesthesia, stereotactic neurosurgical creation of a burr hole and passage of a probe through brain tissue to the target, followed by implantation of the DBS electrode, with intraoperative stimulation to ensure the absence of significant adverse effects;
- Under general anesthesia, surgical tunneling of the lead extension wires (from the scalp to the upper chest area) and implantation of pulse generator in the chest wall, followed by programming of the stimulator

#### **FDA Status**



An existing national noncoverage policy for the treatment of motor function disorders with electric nerve stimulation is detailed in CIM section 35-20 (Treatment of Motor Function Disorders with Electric Nerve Stimulation - Not Covered). In March 1997, CMS amended this policy to note that:

"Medicare coverage of deep brain stimulation by implantation of a stimulator device is not prohibited. Therefore, coverage of deep brain stimulation provided by an implanted deep brain stimulator is at carrier's discretion."

#### **Timeline of Recent Events**

October

On August 17, 2001, CMS received a letter and a packet of information, including scientific literature, from Barry Green, Ed.D., of Dallas, TX, requesting that the Coverage and Analysis Group (CAG) review bilateral STN stimulation for Parkinson's disease for a Medicare national coverage determination. CMS staff worked with Dr. Green to complete this formal request, including gathering the appropriate evidence, and formally accepted his request for review.

19, 2001	Initiation of formal review process and afficience posted on erro website.
December 13, 2001	CMS requested that the Agency for Healthcare Research and Quality (AHRQ) purchase a technology assessment of bilateral deep brain stimulation of the STN or the GPi for treatment of advanced Parkinson's disease recently performed by the Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA TEC).
January 7,	CMS expanded its evaluation of the evidence to include DBS for essential tremor and Parkinsonian

Initiation of formal review process and timeline posted on CMS website

tremor. The title of this determination was changed to "Deep Brain Stimulation for Parkinson's Disease."

March 8, Issue was referred to the Medicare Coverage Advisory Committee (MCAC), Medical and Surgical Procedures Panel.

NCAC Medical and Surgical Procedures Panel held in Baltimore MD

June 12, MCAC Medical and Surgical Procedures Panel held in Baltimore, MD. 2002

September MCAC Executive Committee (EC) meeting held in Baltimore, MD. 25, 2002

November MCAC EC minutes received by CMS. 1, 2002

#### **General Methodological Principles of Clinical Study Design**



medication.

Patients are assessed at two intervals. The first state is referred to as the "off" medication state, which is that
condition observed after a patient has received no antiparkinsonian medications for 12 hours. This testing is
typically conducted before the patient has taken his or her first morning dose of L-dopa and is intended to
replicate the severity of symptoms patients experience in their daily lives as L-dopa becomes less effective and
motor fluctuations become more frequent and severe. The "on" medication state is defined, by convention, as the
best test scores recorded during the day while the patient is taking L-dopa. In some studies, "on" scores are measured during a "best on" state created with a suprathreshold dose of L-dopa.

The Schwab and England scale is an instrument designed exclusively to evaluate performance of activities of daily living. Scoring direction is the reverse of the UPDRS: a score of 100 indicates normal and a score of 0 indicates complete disability. Like the UPDRS, the Schwab and England scale is usually measured in the "off" and "on" states.

The Hoehn and Yahr scale is a measure of a patient's PD state, with disease stages ranging from 0-5 as follows:

- Stage 0: no signs of disease
- Stage 1: unilateral disease, no imbalance
- Stage 2: bilateral disease, no imbalance
- Stage 3: mild to moderate bilateral disease
- Stage 4: severe disability, still able to walk or stand unassisted
- Stage 5: wheelchair bound or bedridden

Evaluation of neuropsychological sequelae of DBS requires a special battery of assessment instruments selected for their minimal dependence on motor function. Evaluation must be conducted in a manner that minimizes such variables as fatigue and motor symptoms, at a standard time of day when patients are in their best state. Understanding of these evaluations may be further improved by application of statistical techniques for analyzing longitudinal, repeated measures.

Unilateral and Bilateral Thalamic (VIM) DBS Evidence Summary

The BCBSA TEC evaluated DBS of the thalamus for tremor in December 1997. This technology assessment was based on the published literature for patients undergoing implantation of a thalamic stimulation device throughout Europe and North America. Nine studies met study selection criteria (studies must have presented original data, included more than one subject, examined health outcomes, and be published as full-length articles in peer-reviewed journals). The most recently published series from each research group were discussed by BCBSA TEC and are subsequently described in this decision memo. 7.8.9 Evidence from the Medtronic Global Clinical Study Series (1992-1997) was also discussed by TEC but was excluded from TEC's outcomes analyses since some patients in the Medtronic series had already been published separately in the studies described above.

Koller et al (1997) conducted a multicenter trial, involving four clinical sites, of unilateral thalamic (VIM) DBS in 29 ET patients and 24 PD patients with tremor of marked severity resulting in significant disability despite pharmacological treatment. Mean age was 66.8 years for ET patients and 65.4 years for PD patients. ET was diagnosed by postural or kinetic tremors of the hands without other neurologic signs. The diagnosis and selection criteria for PD patients included the presence of 2 cardinal signs (tremor, bradykinesia, rigidity) plus sustained responsiveness to L-dopa and absence of signs of other parkinsonian syndromes. Fifty-three of 59 patients received implantation in the VIM. Six patients were not implanted or not followed, including 2 whose tremor was not suppressed by intraoperative stimulation, 1 intracranial hemorrhage during surgery, 1 persistent microthalamotomy effect, 1 subdural hemorrhage and 1 withdrawal of consent. The study's primary outcome was tremor suppression evaluated with the Tremor Rating Scale for ET and the UPDRS for PD. Patients were blinded to stimulation on or off at 3 months after surgery and with open-label (nonblinded) follow-up evaluations at 6, 9 and 12 months.

With stimulation on, there was significant decrease in contralateral tremor for ET and PD patients at each evaluation (3, 6, 9 and 12 months), with 9/29 (31%) of ET patients and 14/24 (58%) of PD patients experiencing total tremor resolution. Among secondary functional outcomes, motor performance skills significantly improved at 3 months only in the ET patients. Subjective assessment of global disability showed moderate to marked improvement in 71% of ET and 90% of PD patients.

Benabid et al (1996) reported on 117 consecutive patients with severe tremor, including 80 PD and 20 ET patients implanted with unilateral or bilateral thalamic (VIM) electrodes from 1987 through 1994. Mean age of patients, duration of illness and statistical analyses were not reported. Results indicated that tremor was the only symptom significantly influenced by thalamic (VIM) DBS, that rigidity was only slightly affected due to the tremor suppression, and that there was almost no change in bradykinesia or other symptoms of PD. During the initial 3-month postoperative period, there was either complete disappearance or only rare reappearance of tremor in 102 (91.9%) of the 111 operated sides. The effect of VIM stimulation remained stable in 96% of stimulated sides in PD and in 81% of stimulated sides in ET.

In PD patients, tremor was selectively suppressed for as long as 8 years. In ET patients, results were satisfactory but deteriorated over time in 18.5% of cases. 31.6% of patients experienced minor postoperative side effects, but there was no operative mortality or permanent morbidity. Neither simultaneous bilateral thalamic implantation performed in 38 PD and 13 ET patients, nor complementary implantation on the contralateral side of a previous contralateral thalamotomy performed in 8 PD and 2 ET patients, induced any of the neuropsychological deficits reported for bilateral thalamotomy.

Alesch et al (1995) reported on 23 idiopathic PD and 4 ET patients treated with thalamic (VIM) DBS for medically refractory tremor severely impairing most routine activities. Mean age was 65 years and mean duration of illness was 13 years. Five PD patients had previous thalamotomy more than 5 years before with sustained success. The study's primary outcome was tremor suppression evaluated by the UPDRS and the Essential Tremor Rating Scale measured preoperatively and repeated at 3, 6 and 12 months postoperatively. Twenty-seven patients were implanted unilaterally and 6 patients bilaterally, for a total of 33 operated sides.

Tremor suppression was complete in 21/33 (64%) of implanted thalami and showed major improvement in 6/33 (18%), minor improvement (marked but less pronounced tremor remaining) in 4/33 (12%) and no improvement in 2/33 (6%). Using the UPDRS subscales, patients undergoing stimulation also showed a mean improvement of 45% on the ADL score and an improvement of 43% on the motor score. There was one intraoperative subdural hematoma, one ischemic infarct and no infections. Neurostimulation side effects included permanent paresthesias in two patients, plus dysequilibrium in one, slight dysarthria in four and marked dysarthria in two patients. Within that last category, one of six patients implanted bilaterally experienced marked but reversible dysarthria under stimulation, which was directly proportional to the stimulation voltage. Despite this side effect, the patient preferred dysarthria to tremor. Study follow-up ranged from 3-48 months and reported improvements were durable in all cases.

Medtronic's Global Clinical Study Series was presented to the FDA Neurological Devices Panel in March 1997 and was summarized briefly by BCBSA TEC. In that multicenter study of 347 patients undergoing implantation of 406 DBS systems, 12% of patients experienced complications attributed to the device and 17% of patients experienced complications related to the surgical procedure. Thirteen (4%) of the 347 patients had intracranial hemorrhage, including five serious hemorrhages and one postoperative death. Of the 145 (61 ET and 84 PD) of the 347 patients followed for 12 months or more after implantation, over 80% experienced sustained tremor suppression.<sup>10</sup>

TEC determined that unilateral thalamic DBS for patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease met the following five criteria: 1) the technology had final approval from the appropriate government regulatory bodies; 2) the scientific evidence permitted conclusions concerning the effect of the technology on health outcomes; 3) the technology improved the net health outcome; 4) the technology was as beneficial as any established alternatives; and 5) the improvement was attainable outside the investigational settings.<sup>11</sup>

#### CMS Supplemental Review

CMS reviewed the existing literature and performed an updated search of studies published since 1997 regarding thalamic stimulation for essential or Parkinsonian tremor. Inclusion criteria included all studies reviewed as part of the December 1997 BCBSA TEC technology assessment, as well as studies identified in a PubMed database search using keywords "Parkinson\*" and "deep brain stimulation". CMS's search was restricted to English language publications and human studies with at least 10 subjects. Reference lists of retrieved publications were additionally reviewed. As noted by the TEC, several studies seemed to evaluate patients included in previously published literature. Therefore, CMS's descriptions of unilateral thalamic stimulation studies were restricted to only the most recently published studies. Sixteen studies were identified for review and are summarized in Appendix A. Among those 16 studies, two large multicenter series (published since the 1997 BCBSA TEC assessment) described symptomatic improvement of tremor in both PD and ET patients treated with unilateral and bilateral thalamic (VIM) DBS. 12,13

Krauss et al (2001) conducted a multicenter trial of unilateral and bilateral thalamic (VIM) DBS in 94 patients with disabling tremor, including 45 PD and 42 ET patients (plus 7 patients with kinetic tremors of different causes). Electrodes were implanted unilaterally in 65 patients and bilaterally (either simultaneously or staged) in 29. Mean age was 68.7 years. Mean duration of disease and prior surgeries were not reported. The study's primary outcome was improvement in tremor assessed by a standard protocol including the UPDRS for PD patients and the Unified Tremor Rating Scale or modified Clinical Tremor Rating Scale (CTRS) for ET patients. The mean follow -up period was 11.9 months (range 3-24 months).

In PD patients, symptomatic improvement in tremor at the last available follow-up was rated as excellent in 51%, marked in 36%, moderate in 11% and minor in 2%. In ET patients, results indicated symptomatic improvement in tremor rated as excellent in 57%, marked in 36%, moderate in 5% and minor in 2%. Forty of 94 patients experienced stimulation-related side effects which were generally mild and reversible with a change in electrical parameters. These were more frequent in bilateral (52%) than unilateral (31%) DBS patients. There was no persistent morbidity related to surgery and there were no infections.

Limousin et al (1999) reported on a 12 month follow-up of 73 idiopathic PD and 37 ET unilaterally or bilaterally implanted thalamic (VIM) DBS patients with pharmacotherapy resistant tremor operated on in 13 European neurosurgical centers. The selection of patients was limited to those whose tremor scale rating was marked or severe for the limb intended for treatment and those capable of abiding by the protocol and operating the stimulator. Patients were excluded from the study if they had a previous thalamotomy on the implanted sided, significant brain atrophy or structural damage seen on CT or MRI, marked cognitive dysfunction, active psychiatric symptoms, or concurrent neurological or other uncontrolled medical disorders. In PD patients, mean age at implant was 61.5 years and mean duration of disease 10 years. Fifty-seven PD patients were implanted unilaterally and 16 bilaterally. In ET patients, mean age at implant was 63.1 years and mean duration of disease 26.6 years. Twenty-eight ET patients were implanted unilaterally and 9 bilaterally.

Results indicated that both upper and lower limb tremor were significantly reduced in PD patients at 3 and 12 month follow-up. In ET patients, stimulation significantly reduced postural and action tremor of the upper and lower limb at 3 and 12 months, but head tremor was significantly improved only at 3 month follow-up. The number of patients using medications was not changed and the mean medication doses were not significantly reduced at 12-month follow-up. 4 patients had major adverse events unrelated to surgery (3 deaths and 1 stroke), 3 patients had subdural hematomas which resolved, 2 patients had subcutaneous hematomas which were evacuated, 2 patients had infections requiring temporary explantation, and 5 patients required electrode replacement and repositioning. Other adverse effects, including dysarthria (7), disequilibrium (3) and dystonia (1) were mild and reversible with change of stimulation parameters.

Also among the 16 studies in Appendix A is a relevant comparison of unilateral and bilateral thalamic DBS published since the 1997 BCBSA TEC assessment. In this study, Ondo et al (2001) reported on 13 ET and 8 tremor-dominant PD patients who underwent staged bilateral thalamic (VIM) DBS. Study outcomes compared both efficacy and adverse events 3 months after initial thalamic DBS implant with those 3 months after contralateral thalamic DBS placement. Mean age was 71.5 years for ET patients and 71.4 years for PD patients. All ET patients and 6 of 8 PD patients elected to initially have their dominant side implanted. The ET evaluation included subjective questions based on the Unified Tremor Rating Assessment, clinical assessments of arm, leg, voice, head, face and tongue tremors, as well as drawing, writing and water pouring tests on both sides. PD patients were primarily evaluated with the UPDRS.

After the second thalamic implantation, overall results indicated all specific measures assessing tremor contralateral to that side improved in both ET and PD patients, generally without sacrificing the improvements to the first side implanted. Midline tremors of the face and head improved only after the second implantation. PD patients had less subjective improvement than ET patients in their functional and subjective scores after the second implantation, but the authors noted their relatively small sample size, short period of evaluation and inability to control for disease progression. Adverse events were described as generally mild to moderate, but more frequent in ET patients (92%) than PD patients (50%) and more frequent in bilateral (76%) than unilateral (52%) implantation. The most problematic stimulation-related adverse effects were gait disorders and dysarthria. There were no serious perioperative adverse effects.

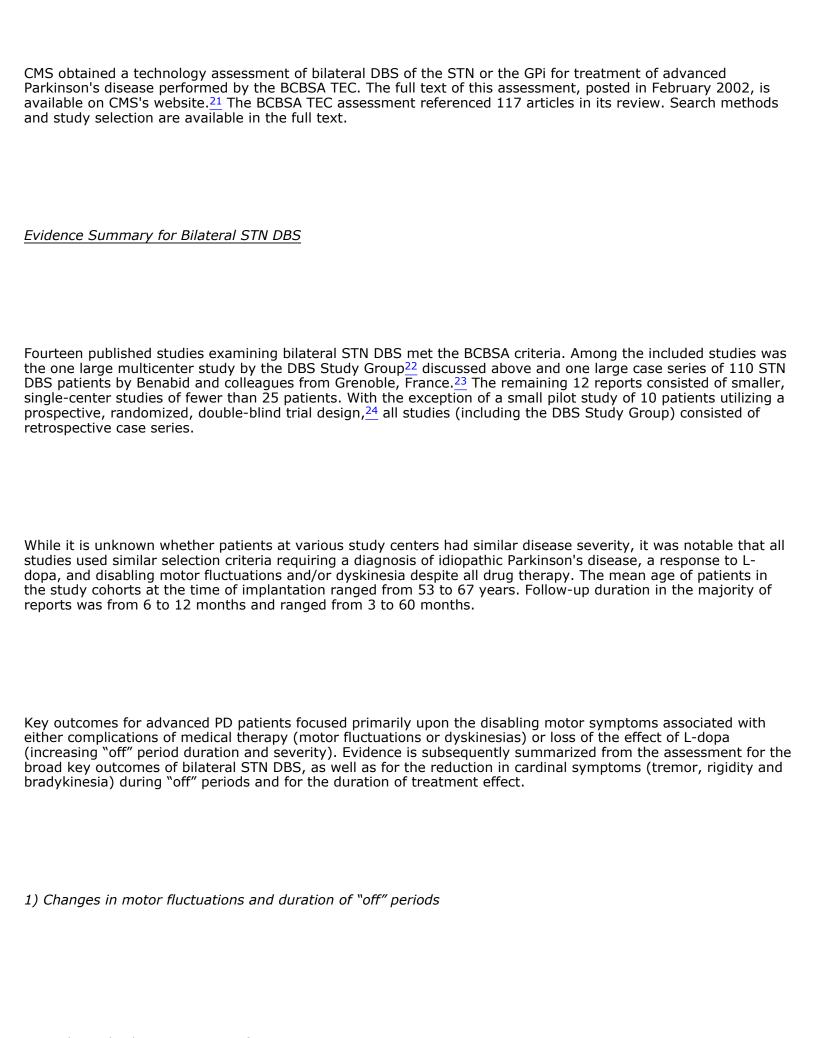
<u>Unilateral and Bilateral Subthalamic Nucleus (STN) and Globus Pallidus Interna (GPi) DBS Evidence Summary</u>

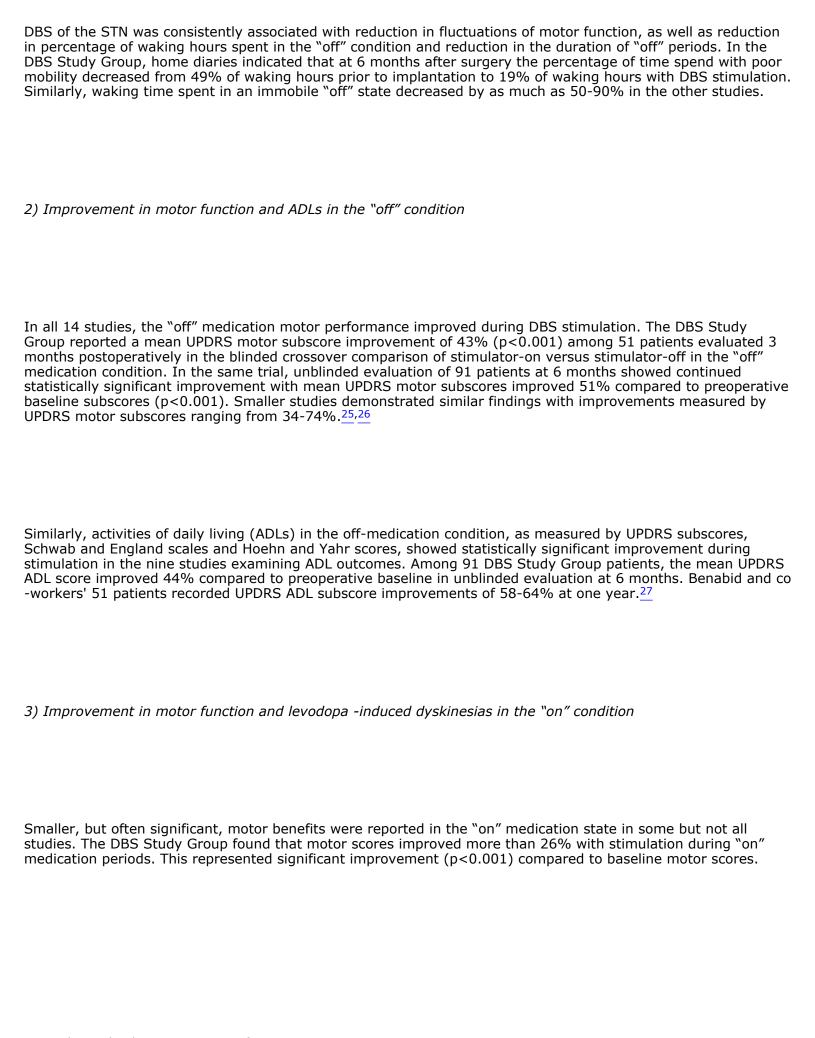
The largest clinical series of bilateral DBS was a multicenter study by the "Deep Brain Stimulation for Parkinson's Disease Study Group (DBSPDG)." This study reported on 143 patients enrolled at 18 centers (including 4 within the U.S.) between July 1995 and July 1999. 15 Of note, evidence presented to the March 2000 FDA Neurological Devices Advisory Committee reported on 159 patients enrolled in this study. 16,17,18,19 Assignment to either bilateral STN or GPi DBS was according to the operating neurosurgeon's preference and not all centers performed both STN and GPi procedures. Patients ages ranged from 30-75 years and each patient had at least 2 cardinal features of Parkinsonism (tremor, rigidity and bradykinesia), a good response to L-dopa, a motor score of >30 on the UPDRS when off medication, and motor complications that could not be controlled by pharmacologic therapy. Mean age at surgery was 59.6 years for STN patients and 55.7 years for GPi patients. Nine of the 143 patients enrolled (6 in the STN group and 3 in the GPi group) did not receive bilateral DBS because of complications in the initial unilateral DBS implantation, including intracranial bleed, paresis, confusion, lack of response to DBS and improper lead placement.

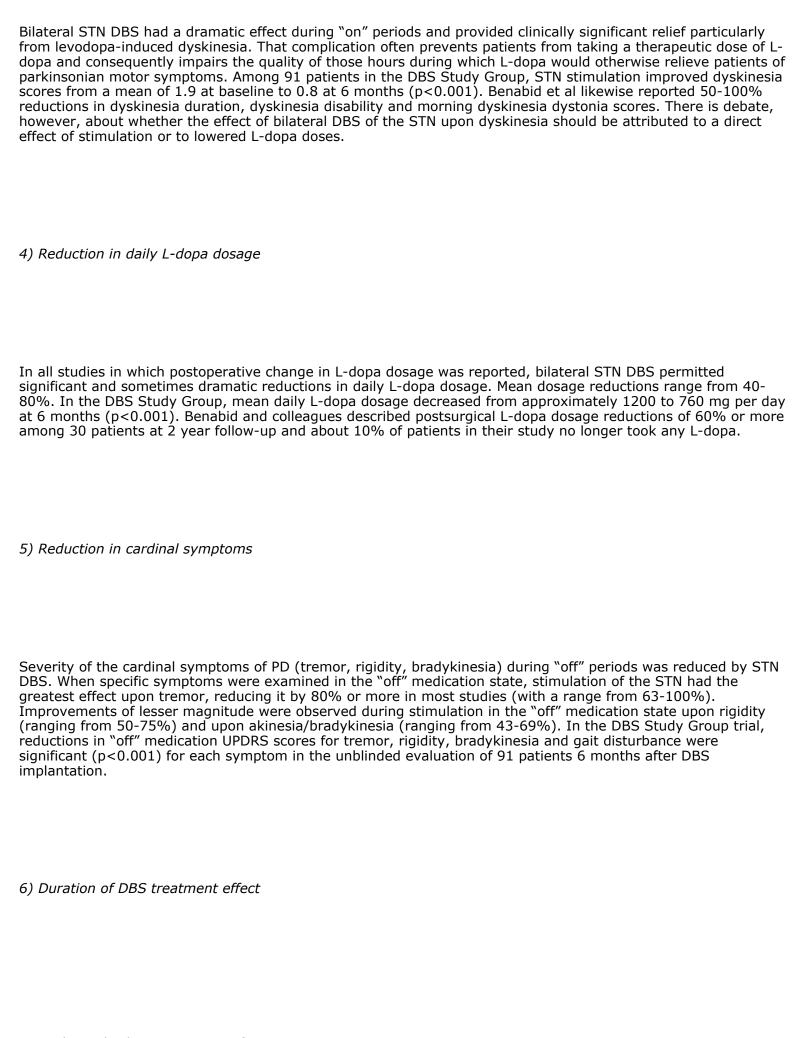
Analysis of the 134 patients bilaterally implanted excluded 5 of 102 patients in the STN group who did not participate in the 3 month blinded evaluation or the 6 month follow-up (2 with infected leads and 3 who withdrew consent), excluded 3 of 41 patients in the GPi group who did not participate in the 3 month blinded evaluation (2 refused and 1 withdrew), and also excluded an additional 2 of 41 patients in the GPi group who did not complete 6 month follow-up (1 withdrew and 1 died of esophageal carcinoma). The DBS Study Group thus evaluated 126 of 134 bilaterally implanted patients in blinded 3 month motor assessments and 127 patients in unblinded 6 month self-reported home diary assessments. Considering omission of slightly greater than 10% of the 143 patients enrolled in this study (or slightly greater than 20% of the 159 patients reviewed by the FDA panel), the DBS Study Group's lack of intention-to-treat analysis may have resulted in an overestimation (or underestimation) of their primary and secondary outcomes.

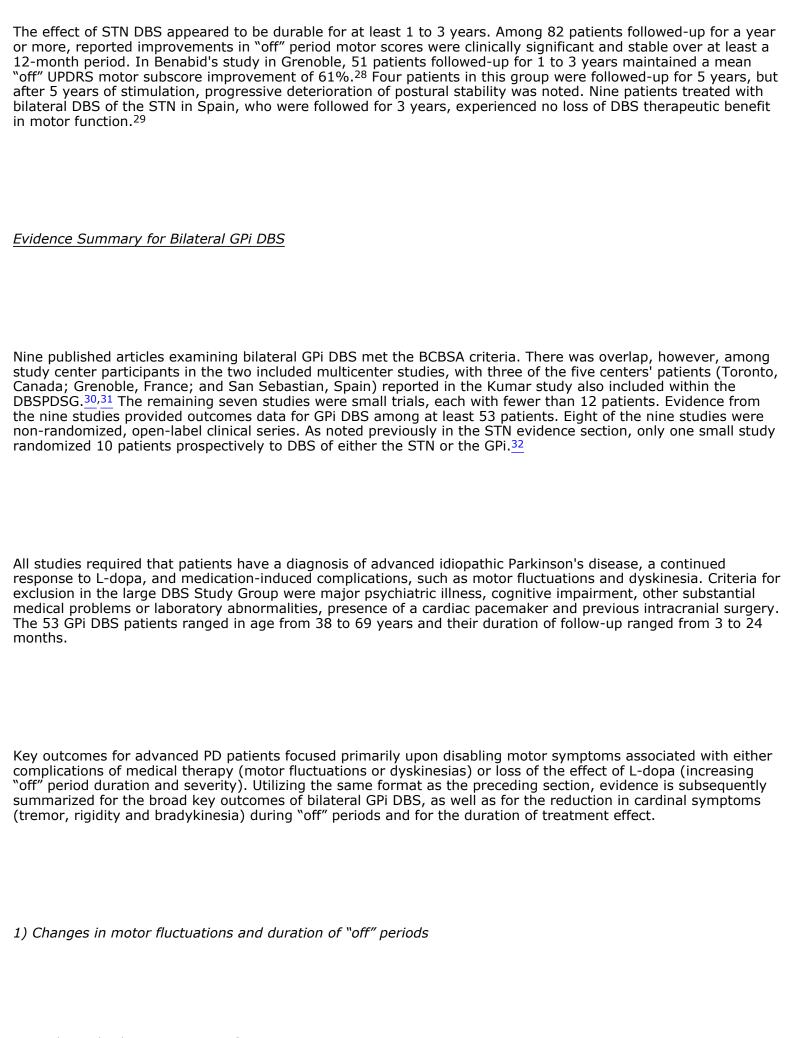
The DBS Study Group's primary outcome was mean improvement in patients' UPDRS motor subscores after having received two hours of deep brain stimulation. Patients were assessed at 3, 6 and 12 months postoperatively. The randomization was to whether stimulation was "on first, then off" or "off first, then on" prior to measurement, and only at the 3-month assessment were patients and observers blinded to whether or not the stimulator was turned on or off. Stimulation was associated with a mean improvement in UPDRS motor subscores of 43% in the STN group and 32% in the GPi group compared to evaluation performed without stimulation. There was median improvement of greater than 25% in the UPDRS motor subscores at 15 of 16 centers performing the STN procedure and at 9 of 10 centers performing the GPi procedure. Unblinded secondary outcomes included the percent time in waking hours with poor mobility ("off" state) versus good mobility ("on" state) either with or without dyskinesias (involuntary movements). These were recorded in a home diary at the preoperative baseline and at 1, 3 and 6 months postoperatively. Between the pre-op baseline and 6 month follow-up, the self-reported improvement in the percent time with good mobility in the "on" state without dyskinesia increased from 27% to 74% for the STN group and from 28% to 64% for GPI group. Results and complication rates were not stratified by age or center. Among the DBS Study Group's 143 patients, serious adverse events included 7 intracranial hemorrhages, 4 infections (including 2 lead removals), 5 lead migrations and 4 persistent neurologic deficits. Total adverse events were not reported by the DBS Study Group. For all 159 patients reviewed by the March 2000 FDA advisory committee, 87.4% of patients experienced one or more adverse events (ranging from minor device related complications to major intracranial hemorrhage) and 52.2% of patients experienced one or more serious adverse events.20

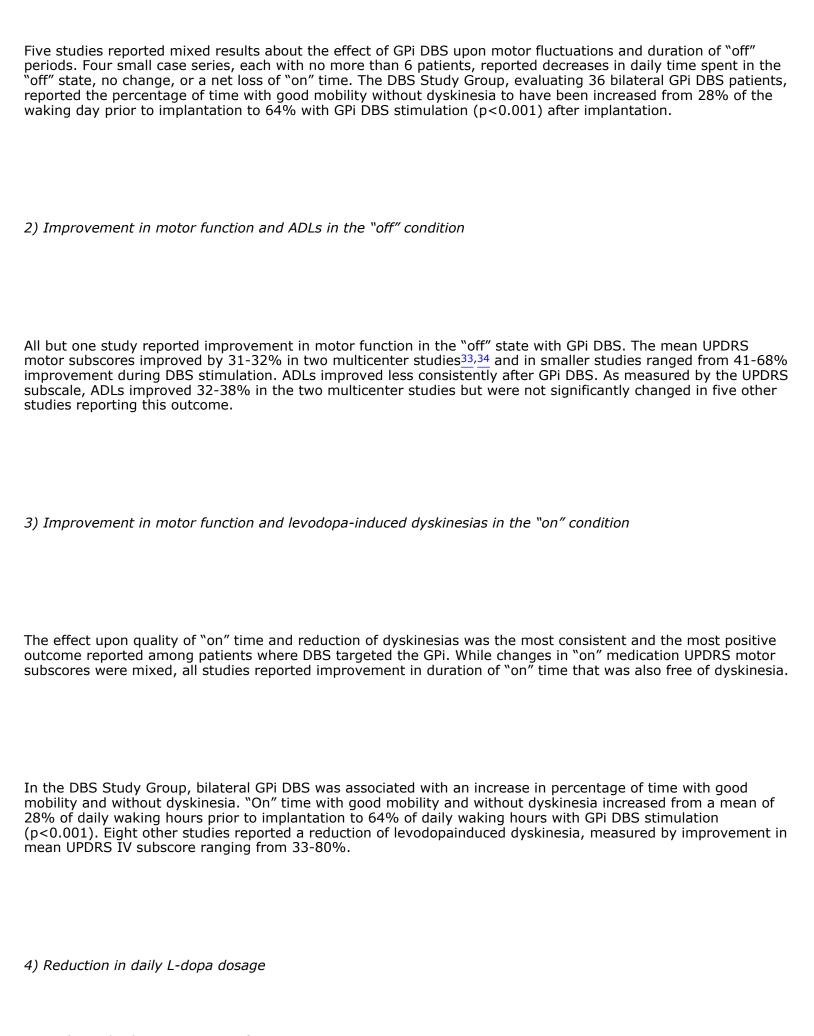
2002 BCBSA TEC Technology Assessment

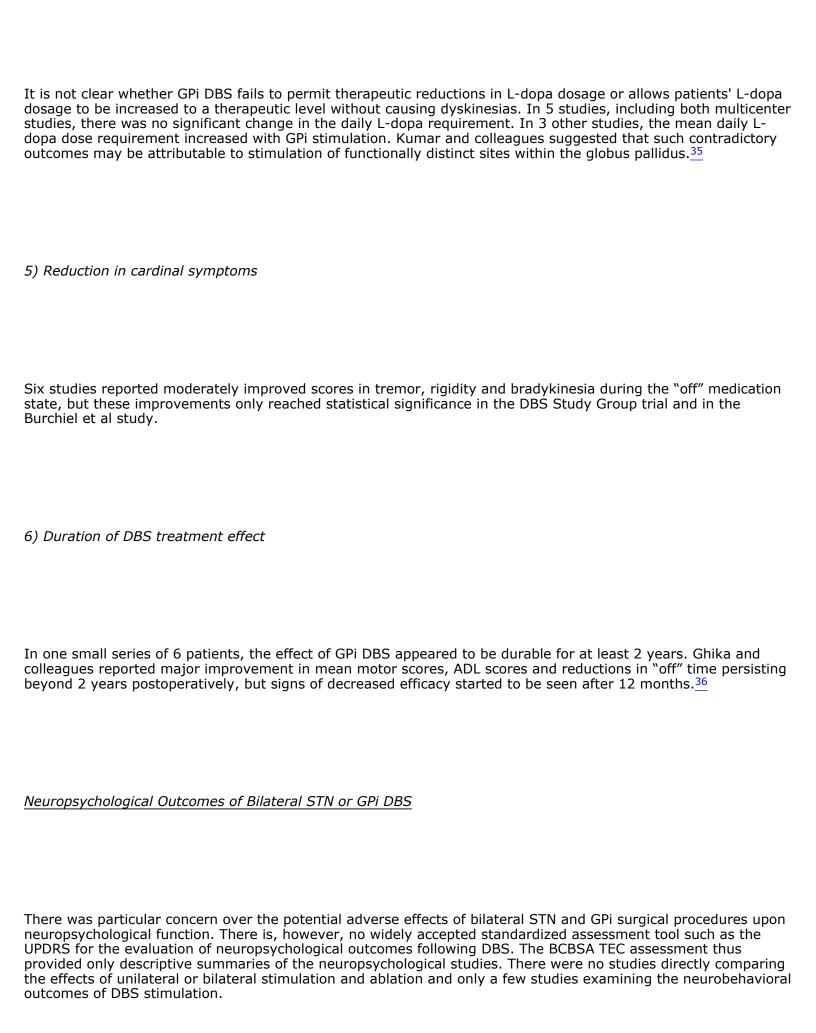












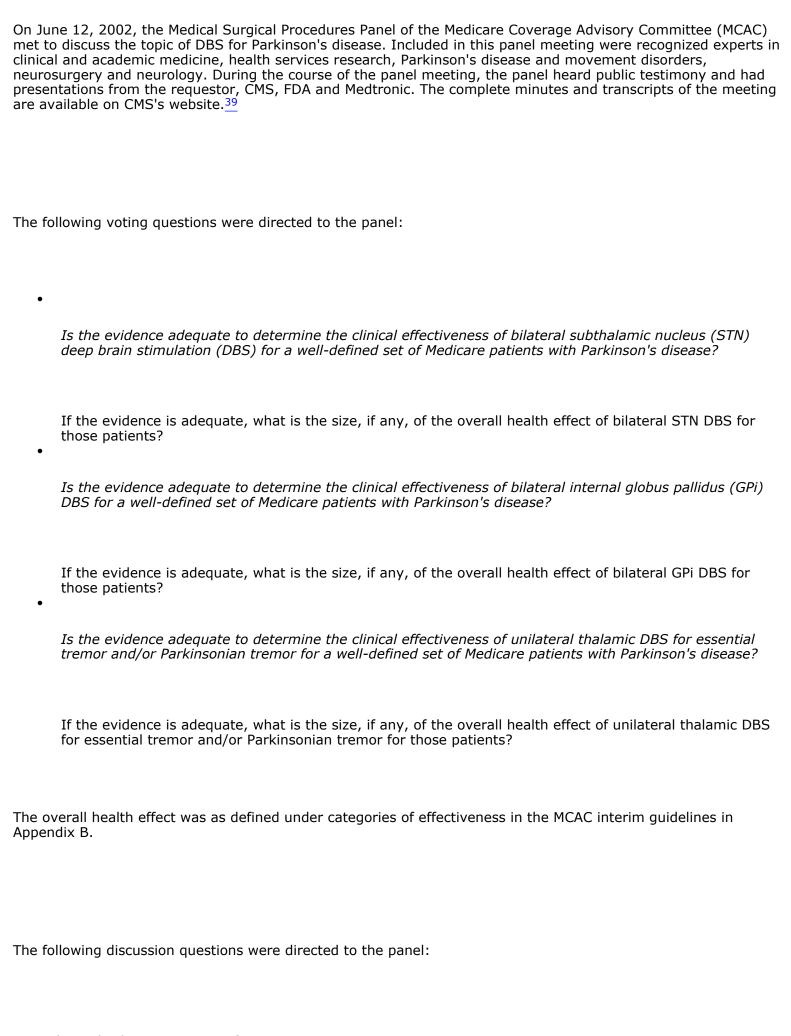
Evidence shows that laterality of a surgically created lesion is a significant determinant of neuropsychological sequelae, such as loss of verbal and visuospatial abilities after unilateral pallidotomy. Additionally, some patients pleased with pallidotomy's motor outcomes were often restricted in their ability to function properly at work or in social settings. Ten studies addressing whether bilateral DBS posed this same risk were evaluated in the BCBSA TEC assessment. There was great variation among these studies in terms of design, extent to which patients were characterized at preoperative baseline, the neuropsychological and psychiatric measures employed, the frequency of and interval between examinations, the inclusion of a control group and methods used for statistical analysis.

If only the most recent publication from each medical center was considered, neuropsychological evaluation was available for 139 patients with advanced Parkinson's disease treated with DBS of either the STN or the GPi. Although studies varied in their assessment of the degree of neuropsychological risk associated with DBS, there appeared to be some consensus that the risk, while present, was minimal. Common to nearly all studies was the finding of some degree of compromise in the realm of verbal learning and/or language fluency after implantation of DBS electrodes. Noting that, in general, all surgical procedures for Parkinson's disease involving the left or both hemispheres appeared to negatively affect verbal memory, it was concluded that, since the involved nuclei are related to memory processes, some change in learning ability after these surgical procedures was to be expected.

Summary of Technology Assessment Conclusions According to TEC Criteria

TEC determined that bilateral DBS of the STN or GPi for the treatment of advanced Parkinson's disease met the following BCBSA TEC criteria: 1) the technology had final [conditional] approval from the appropriate government regulatory bodies; 2) the scientific evidence permitted conclusions concerning the effect of the technology on health outcomes; 3) the technology improved the net health outcome; 4) the technology was as beneficial as any established alternatives; and 5) the improvement was attainable outside the investigational settings.

**MCAC Medical and Surgical Procedures Panel** 



•	
Available clinical evidence evaluates bilateral STN or GPi DBS in early onset Parkinson's Can these results be generalized to late onset advanced Parkinson's disease patients?	disease patients.
• For coverage purposes, should Medicare patients be considered candidates for unilateral bilateral STN or GPi DBS only if their characteristics closely match those of the patients available studies?	
• DBS in the clinical literature is performed by highly trained providers at experienced facility and provider criteria to perform DBS in Medicare patients be part of any positive decision?	lities. Should coverage
Panel Conclusions for Unilateral Thalamic DBS	
The MCAC panel voted that the evidence was adequate to determine the clinical effectiveness of thalamic [VIM] DBS for essential tremor and Parkinsonian tremor for a well-defined set of Medi Parkinson's disease.	of unilateral care patients with
Prior to voting on levels of effectiveness, the panel discussed the differences between "breakthe and "more effective." Some panelists stated that in some ways this technology may have representation breakthrough, as in a major advance in treatment, but it did not rise to the level of standard of felt that it had more than small effects, as in the definition of "more effective" provided by the Committee. Following this discussion, the panel voted unanimously to temporarily create a new effectiveness, falling between "breakthrough" and "more effective." They voted in favor of a stain improves health outcomes by a substantial margin as compared with established services or metallic than the panel voted in favor of a stain proves health outcomes by a substantial margin as compared with established services or metallic than the panel voted in favor of a stain proves health outcomes by a substantial margin as compared with established services or metallic than the panel voted in favor of a stain proves health outcomes by a substantial margin as compared with established services or metallic than the panel voted in favor of a stain proves.	sented a care. They also Executive category of atement that it
Panel Conclusions for Bilateral STN and GPi DBS	

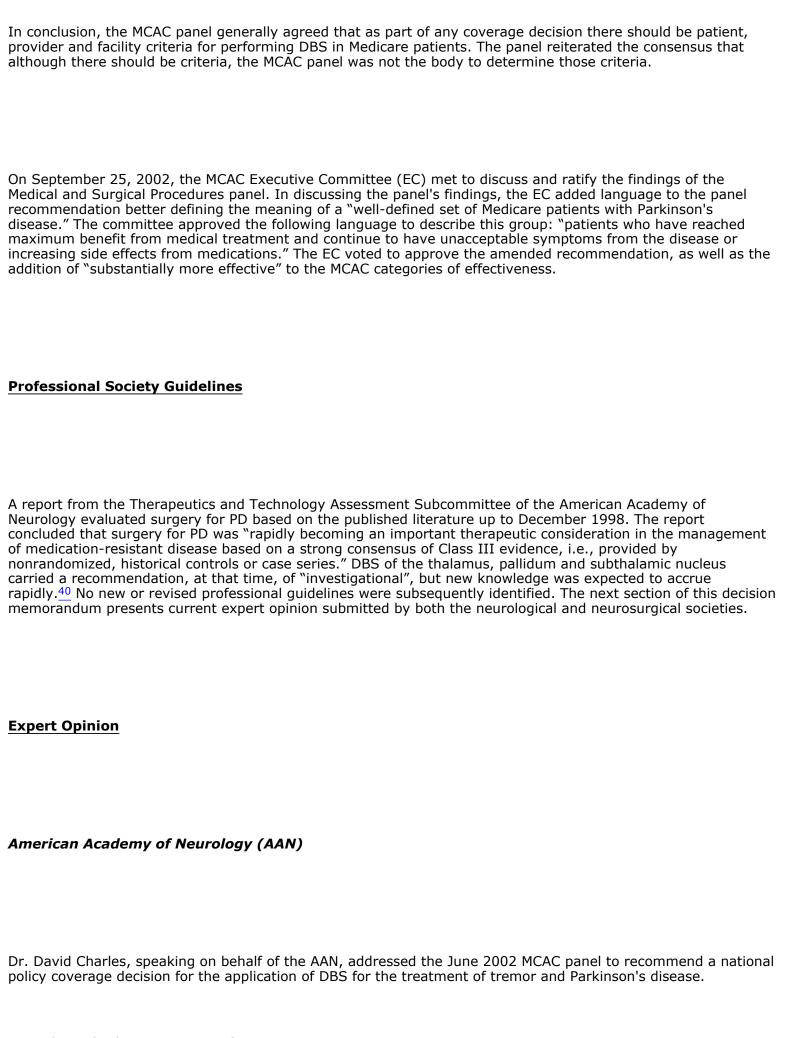
The panel	voted that	the evidence	was adequate	to determ	ine the clinica	l effectiveness	of bilateral	STN DBS	and
bilateral G	Pi DBS for	a well-defined	set of Medica	are patients	s with Parkins	on's disease. 1	The panel lik	kewise	
concluded	that both	STN and GPi D	BS improve h	ealth outco	omes by a sub	stantial margi	n.		

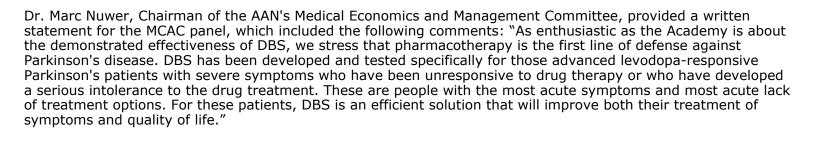
#### Panel Discussion

The panel noted that tremor may be unilateral or bilateral or one side may predominate in ET and PD patients with disabling tremor. The panelists, therefore, also discussed the utility of both unilateral and bilateral (VIM) thalamic DBS. Neurosurgeon panelist Dr. Burchiel disagreed with the BCBSA assessment's statement that bilateral thalamic stimulation was not done because of untoward effects on oropharyngeal musculature, dysphasia and dysarthria. While difficult to ascertain from the literature whether the bilateral procedures had been done simultaneously or sequentially (staged), in practice it was noted that after having unilateral DBS for the side predominantly affected by tremor, the patient often responds so well that he or she seeks the procedure on the other side. In these cases, simultaneous implantation may not be as warranted or as desirable as staged bilateral thalamic DBS. Neurosurgeon panelist Dr. Follett strongly concurred that bilateral thalamic stimulation is done quite effectively, that actual practice today deals with bilateral stimulation, and that it would do some of their patients [with bilateral tremor] a real disservice to restrict thalamic DBS to unilateral applications.

A number of panelists expressed concern that the skill and training of practitioners may affect health outcomes. In response to a question regarding marketing of the procedures, Medtronic stated that the decision to recommend treatment is reached through a team approach for each patient, and that any physician doing the procedure would be adequately trained. A concern was also raised regarding whether the patient population benefiting from DBS would be Medicare beneficiaries. After discussion, it was the consensus of the panel that although patients may not be 65 years of age when they have the need for the treatment, they would probably qualify for Medicare coverage by reason of their disability. Therefore, DBS would affect a well-defined segment of the Medicare population.

In addition to discussion regarding the age distribution for DBS results, discussion also ensued regarding additional Medtronic data provided to the panel regarding DBS complications under and over the age of 65 years (See Appendix C). Statistically significant differences were noted for cardiovascular disorders, confusion, paresis, hemiplegia and intracranial hemorrhage, including that hemiplegia (a very significant adverse effect) occurred almost five times as frequently in people over the age of 65 as in people under the age of 65. Overall, while the data submitted for age stratification was felt to be limited, the panel acknowledged that the direction of the evidence appeared to be for continued benefit, but with increased risks of the procedure with advancing age. The MCAC panel also discussed the difficulty in identifying early onset versus late onset PD patients, as well as the duration of disease, severity of disease and response to medications further complicating generalizations of study results from one group to the other.





American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS)

Dr. Frederick Lenz, speaking on behalf of AANS/CNS, addressed the June 2002 MCAC panel to explain the history of DBS and targeting of the thalamus, GPi or STN. Dr. Lenz noted that medications and stimulators are adjusted simultaneously in Parkinson's patients and, in carrying out these procedures, it was essential to have a movement-disorder neurologist determine each patient's diagnosis, decide whether maximal medical therapy had been employed, and adjust the stimulators.

In its written comments for the MCAC panel, the AANS/CNS noted that the BCBSA TEC assessment published in January 2002 had stated that "Because it is associated with a higher incidence of speech, swallowing, and cognitive dysfunction, bilateral DBS of the VIM is seldom performed." The AANS/CNS responded by saying: "We disagree with this statement, as many centers perform bilateral VIM DBS for patients with bilateral tremor 41,42. Although between 3050% of patients will initially have side effects from stimulation, the adjustability and reversibility of the therapy allow virtually all patients to achieve some measure of tremor control with minimal or controllable side effects. If unacceptable side effects persist, the DBS system can be deactivated. DBS therefore represents the only option for patients with severe bilateral tremor. However, most investigators now agree that the results from STN stimulation are superior for Parkinson's disease, and the side effect profile less. Thalamic DBS should thus usually be reserved for Essential Tremor or other non-Parkinsonian tremor disorders, although it may still have a role in rare Parkinsonian patients whose sole disabling symptom is tremor."

The AANS/CNS concluded that DBS has been shown to be "a safe and effective procedure for medically intractable Parkinson's disease and other movement disorders, when performed in appropriate centers." Detailed recommendations (see Appendix D) were also made by the AANS/CNS regarding general indications for DBS, specific indications by target site (VIM thalamus, STN and GPi), contraindications for DBS, and technical criteria for performing DBS.

#### **Ongoing Clinical Trials**

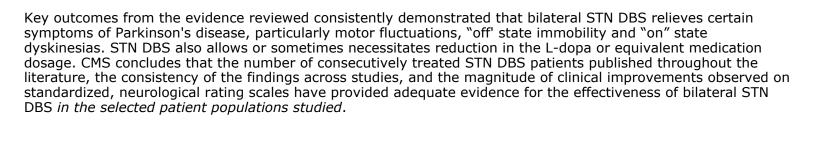
Definitive determination of which stimulation target, the STN or GPi, provides most effective therapy requires a well-designed randomized clinical trial. Such a trial, the Veterans' Administration and NIH's National Institute of Neurological Disorders and Stroke (VA/NINDS) Cooperative Trial, involving six Parkinson's disease centers and their university affiliates, started in 2002 and plans to enroll a total of 300 patients. Patients will be randomized to one of two groups, either immediate DBS surgery or delayed DBS surgery after a six month trial of best medical management. Each surgical group will then be further randomized to either STN or GPi targeting, and all patients will be followed for two years.

## **CMS Analysis**

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act  $\S$  1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."  $\S$  1862(a)(1)(A).

Our analysis focused on the following questions, posed to the June 2002 MCAC panel and subsequently utilized in CMS's decision-making process:

Is the evidence adequate to determine the clinical effectiveness of bilateral STN DBS for a well-defined set of Medicare patients with Parkinson's disease?



For neuropsychological outcomes associated with STN as well as GPi DBS, CMS concludes that the significant motor benefits achieved with bilateral DBS may be accompanied by some adverse neurocognitive effects. These are not comparable, however, to the unacceptably high risks associated with bilateral pallidotomy and it appeared that bilateral DBS's negative impact upon neurobehavioral function was not as clinically meaningful to most patients as the potential motor improvement. For most investigators and patients, the motor benefits of DBS thus appeared to outweigh the neuropsychological risks.

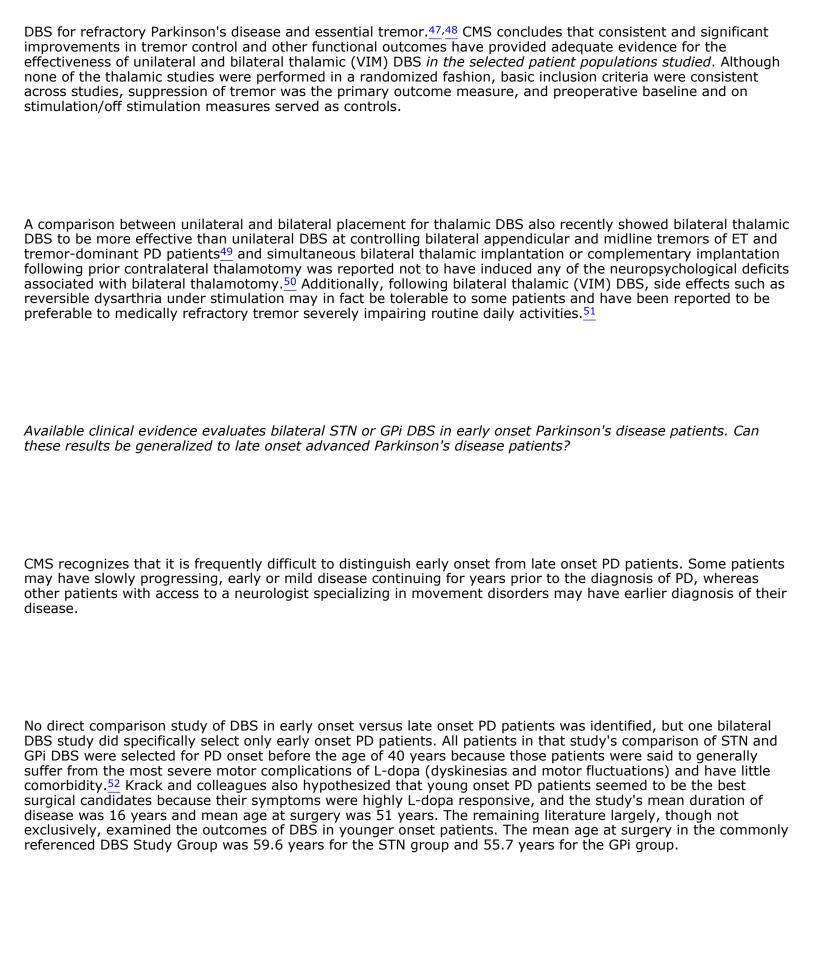
A surgical alternative for patients with medically refractory Parkinson's disease is pallidotomy, but there were no studies directly comparing chronic bilateral STN DBS with pallidotomy. Pallidotomy, however, is limited to a unilateral procedure because of an unacceptably high risk of adverse neuropsychological outcomes if performed bilaterally. The fact that STN DBS can be offered bilaterally is thus advantageous, since PD symptoms most often affect both sides of the body. Unlike the pallidal ablative procedure, STN DBS also has the advantage of being adjustable and reversible (the electrode can be removed).

Patients with advanced, asymmetric PD may initially require only unilateral STN or GPi DBS. These PD patients include those with severe asymmetric tremor who can be effectively treated with unilateral thalamic or STN DBS, as well as those with severe unilateral dyskinesias who can be treated with unilateral GPi DBS. Krause and colleagues noted that STN DBS suppressed tremor as effectively as thalamic VIM DBS and (contrary to thalamic VIM stimulation) caused no tremor rebound when stimulation was switched off. STN DBS could thus be as effective, or possibly even the preferred target, for some patients with either unilateral or bilateral tremordominant PD.<sup>43</sup>

CMS recognizes that there may occasionally be patients with advanced, asymmetric PD who initially require only unilateral STN or GPi DBS. Such patients would include those with severe asymmetric tremor of PD effectively treated with either unilateral thalamic or STN DBS, as well as those patients with severe unilateral dyskinesias that can be treated with unilateral GPi DBS.

Is the evidence adequate to determine the clinical effectiveness of bilateral GPi DBS for a well-defined set of Medicare patients with Parkinson's disease?



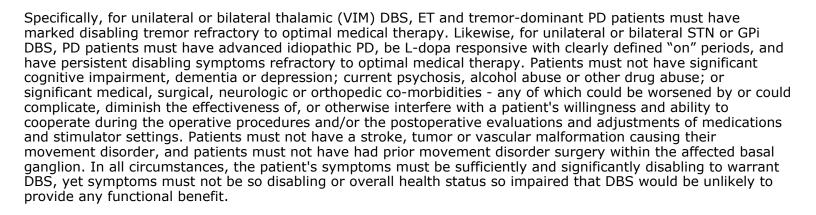


According to testimony before the FDA's Neurological Devices Advisory Committee, the majority of PD patients typically have their onset of disease in the late fifth or early sixth decade, and become significantly refractory to medication in their 60s and 70s. 53 Furthermore, the direction of the evidence (including Medtronic's limited supplemental age stratification data) was for decreased though continued benefit, but increased procedural risks with advancing age. There were statistically significant increases in the rate of complications, especially intracranial hemorrhage and neurologic deficits, for patients over 65 years of age. This was also corroborated by Benabid et al, who emphasized that the complications related to DBS increase exponentially with chronological age. 54 In fact, throughout the published literature, the selection of younger PD patients and exclusion of older Medicare or late onset PD patients tends to maximize the effect size of DBS, while minimizing its risks.

While agreeing that existing data for late onset PD patients was inadequate, expert opinion from the MCAC panel nonetheless suggested that the more critical issue was patients' duration and severity of disease. CMS concludes that while there may be benefit for selected late onset Medicare patients, generalization of currently published DBS results to these late onset advanced PD patients is only feasible when duration of disease, severity of disease, response to medications, comorbidities and overall physiological status are comparable to the patient inclusion and exclusion criteria in the available studies.

For coverage purposes, should Medicare patients be considered candidates for unilateral thalamic or bilateral STN or GPi DBS only if their characteristics closely match those of the patients included in the available studies?

While retrospective case series for both unilateral and bilateral DBS have provided compelling evidence for selected populations, no large well-designed prospective study or RCT has adequately evaluated the risks, benefits and optimal target selection for DBS in a representative sample of elderly Medicare patients. Additionally, the long-term safety and effectiveness of DBS therapy have not been established and FDA's determinations of safety and effectiveness are explicitly limited to the populations studied. In particular, for use in specific populations, current labeling precautions include that safety and effectiveness have not been established for patients with neurological disease origins other than ET or idiopathic PD, with a previous surgical ablation procedure, over the age of 75 years, with dementia, with coagulopathies or with moderate to severe depression. CMS remains concerned regarding the external validity or generalization of the risks and benefits of DBS for Medicare patients and concludes that Medicare patients be considered candidates for thalamic, STN or GPi DBS only if their clinical characteristics closely match the patient selection criteria in the published literature.



Additionally, patients who undergo DBS implantation should not be exposed to any form of diathermy (deep heat treatment including shortwave diathermy, microwave diathermy and ultrasound diathermy) or any type of MRI which may adversely affect the DBS system or adversely affect the brain around the implanted electrodes. DBS should be performed with extreme caution in patients with cardiac pacemakers or other electronically controlled implants which may adversely affect or be affected by the DBS system.

DBS in the clinical literature is performed by highly trained providers at experienced facilities. Should facility and provider criteria to perform DBS in Medicare patients be part of any positive coverage decision?

Regarding facility criteria, CMS concludes that medical centers where DBS is to be performed must have brain imaging equipment (MRI and/or CT) for preoperative stereotactic localization and targeting of the surgical site(s), operating rooms with all necessary equipment for stereotactic surgery, and necessary support services for the intraoperative and postoperative care of all Medicare DBS patients.

Regarding provider criteria, CMS acknowledges that the degree of benefit from DBS is clearly reliant on the proper selection of patients and accuracy in targeting, and that selected centers with experienced operators have reported excellent results for patients with severe Parkinson's symptoms refractory to L-dopa. CMS thus concurs with the AANS/CNS recommendation that DBS procedures should only be performed by neurosurgeons skilled in the techniques of stereotactic and functional surgery, who have been trained in the performance of DBS procedures, and who have been credentialed by their institutions as competent to perform these procedures. CMS also concurs with the MCAC panel that physicians specializing in movement disorders must be involved in the diagnosis, selection and post-procedure care of DBS patients. Operative teams must be experienced with target localization and electrode implantation, as well as the operational and functional characteristics of the device.

#### **Decision**

Effective upon implementation of our national coverage determination, Medicare will cover *unilateral or bilateral thalamic VIM DBS* for the treatment of essential tremor (ET) and/or Parkinsonian tremor and *unilateral or bilateral STN or GPi DBS* for the treatment of Parkinson's disease only under the following conditions:

1.

Medicare will only consider DBS devices to be reasonable and necessary if they are Food and Drug Administration (FDA) approved devices for DBS or devices used in accordance with FDA approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials.

2.

For thalamic VIM DBS to be considered reasonable and necessary, patients must meet all of the following criteria:

a.

Diagnosis of essential tremor (ET) based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor- dominant form

b.

Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.

c.

Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings.

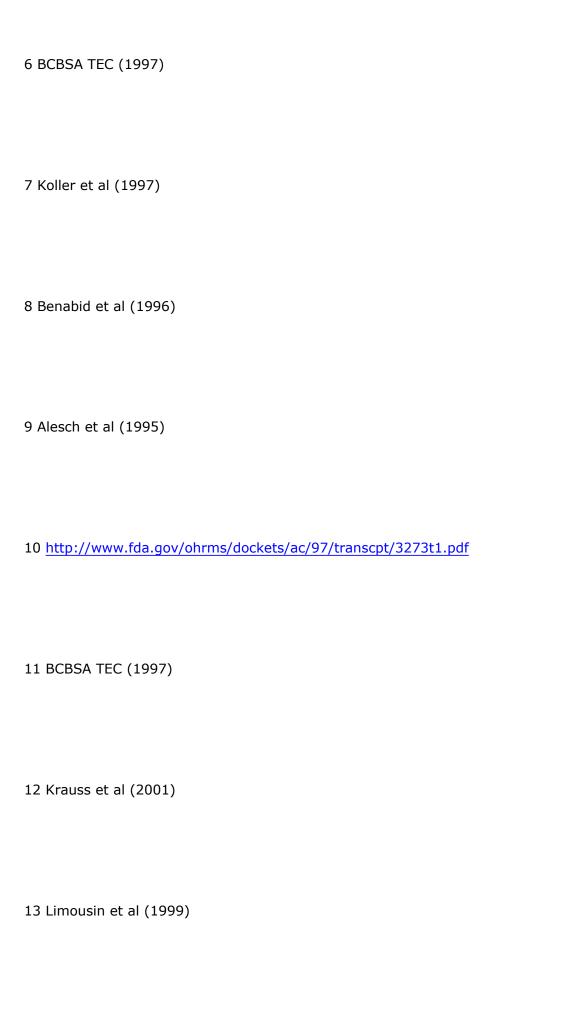
3.

For STN or GPi DBS to be considered reasonable and necessary, patients must meet all of the following criteria:

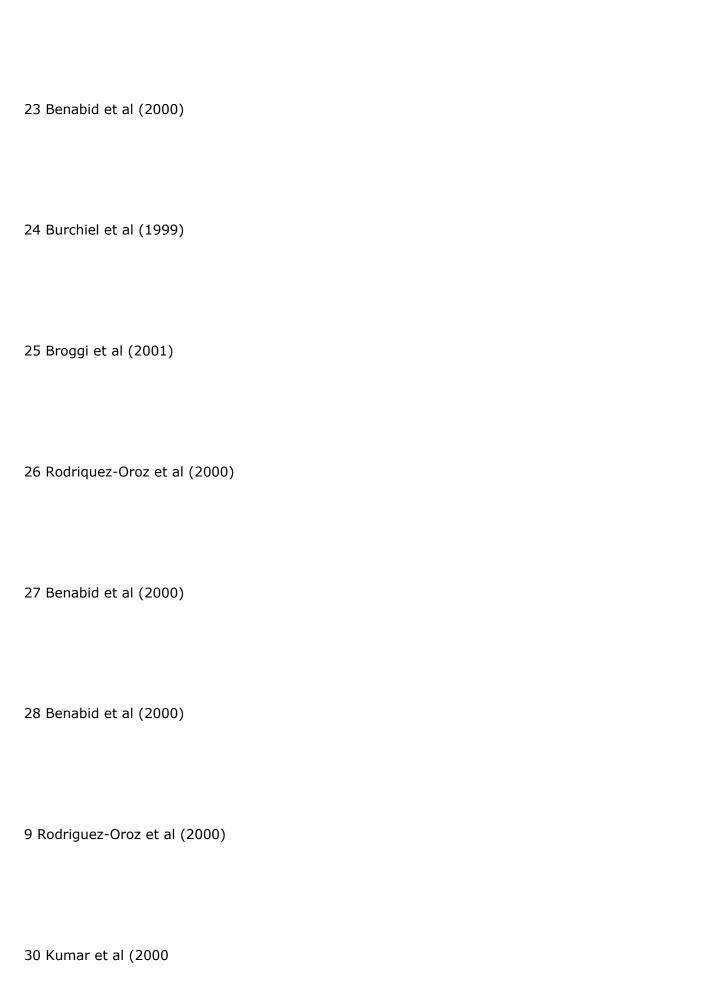
	a.	
		Diagnosis of PD based on the presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia).
	b.	
		Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.
	c.	
		L-dopa responsive with clearly defined "on" periods.
	d.	
		Persistent disabling Parkinson's symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling "off" periods) despite optimal medical therapy.
	e.	
		Willingness and ability to cooperate during conscious operative procedure, as well as during post- surgical evaluations, adjustments of medications and stimulator settings.
DBS is	not re	asonable and necessary and is not covered for ET or PD patients with any of the following:
1. 2.	Non-ic	liopathic Parkinson's disease or "Parkinson's Plus" syndromes.
		tive impairment, dementia or depression which would be worsened by or would interfere with the t's ability to benefit from DBS.
3.		
	Currer	nt psychosis, alcohol abuse or other drug abuse.
4.		
		ural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the nent disorder.

Э.	
	Previous movement disorder surgery within the affected basal ganglion.
6.	Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation.
shortw	ts who undergo DBS implantation should not be exposed to diathermy (deep heat treatment including vave diathermy, microwave diathermy and ultrasound diathermy) or any type of MRI which may adversely the DBS system or adversely affect the brain around the implanted electrodes.
	hould be performed with extreme caution in patients with cardiac pacemakers or other electronically olled implants which may adversely affect or be affected by the DBS system.
For DE the fol	3S lead implantation to be considered reasonable and necessary, providers and facilities must meet all of llowing criteria:
<ol> <li>2.</li> </ol>	Neurosurgeons must: (a) be properly trained in the procedure; (b) have experience with the surgical management of movement disorders, including DBS therapy; and (c) have experience performing stereotactic neurosurgical procedures.
۷.	Operative teams must have training and experience with DBS systems, including knowledge of anatomica and neurophysiological characteristics for localizing the targeted nucleus, surgical and/or implantation techniques for the DBS system, and operational and functional characteristics of the device.
3.	Physicians specializing in movement disorders must be involved in both patient selection and post-procedure care.

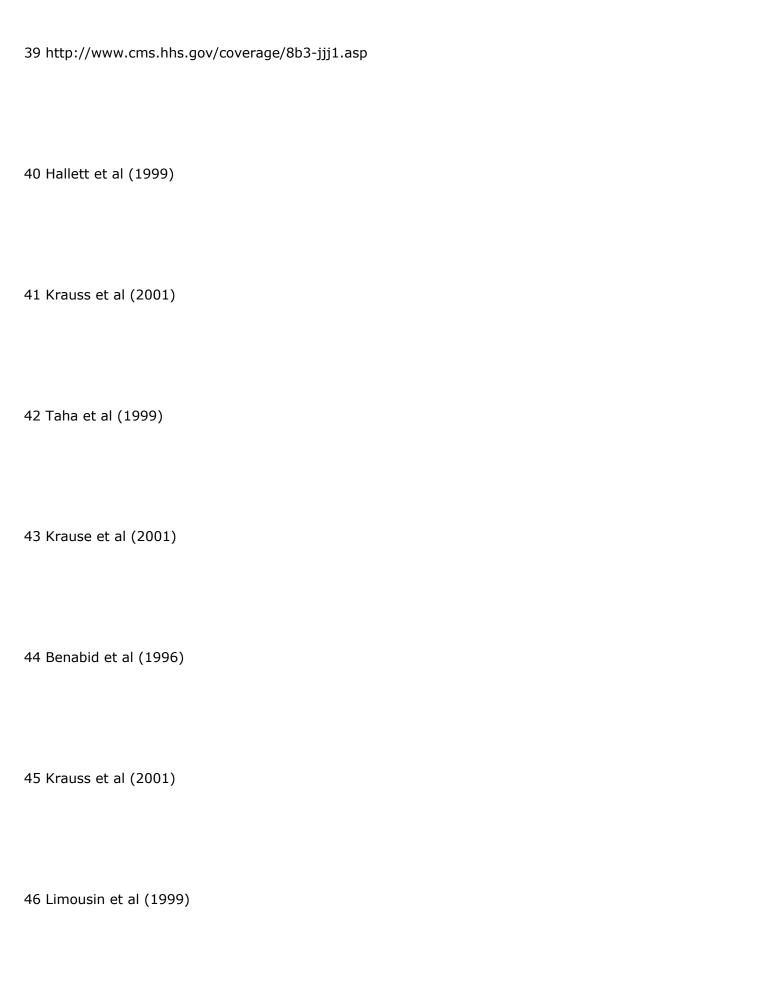
Hospital medical centers must have: (a) brain imaging equipment (MRI and/or CT) for pre-operative stereotactic localization and targeting of the surgical site(s); (b) operating rooms with all necessary equipment for stereotactic surgery; and (c) support services necessary for care of patients undergoing this procedure and any potential complications arising intraoperatively or postoperatively.
Since long-term safety, effectiveness and optimal targeting for DBS have not been established, CMS will review the appropriateness of Medicare coverage as pertinent new evidence becomes available. This review will include clinical follow-up and targeting information from the ongoing, randomized VA/NINDS Cooperative Trial comparing best medical therapy with DBS of the STN and GPi for PD, as well as longer term clinical results from mandatory annual progress reports and final report to the FDA of Medtronic's bilateral DBS PMA postapproval study.
Appendices [PDF, 2MB]
1 Tintner and Jankovic (2002)
2 http://www.medtronic.com/neuro/parkinsons/product.html
3http://www.fda.gov/cdrh/pdf/p960009.pdf
4 <a href="http://www.fda.gov/cdrh/pdf/p960009s7.html">http://www.fda.gov/cdrh/pdf/p960009s7.html</a>
5 Fahn, Tolosa, Marin (1993)

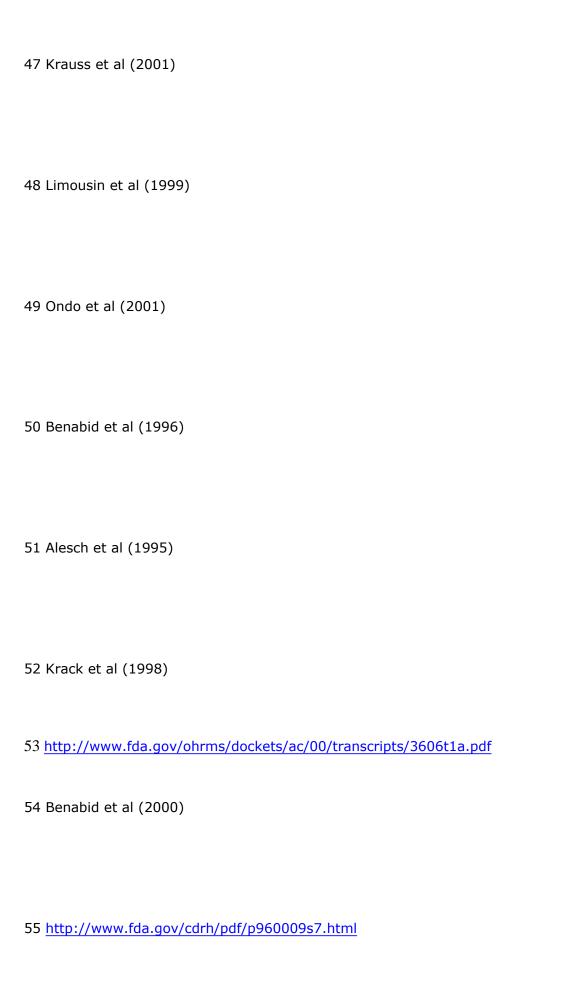






31 DBSPDSG (2001)		
32 Burchiel et al (1999)		
33 Kumar et al (2000)		
34 DBSPDSG (2001)		
35 Kumar et al (2000)		
36 Ghika et al (1998)		
37 Green and Barnhart (2000)		
38 Stebbins et al (2000)		





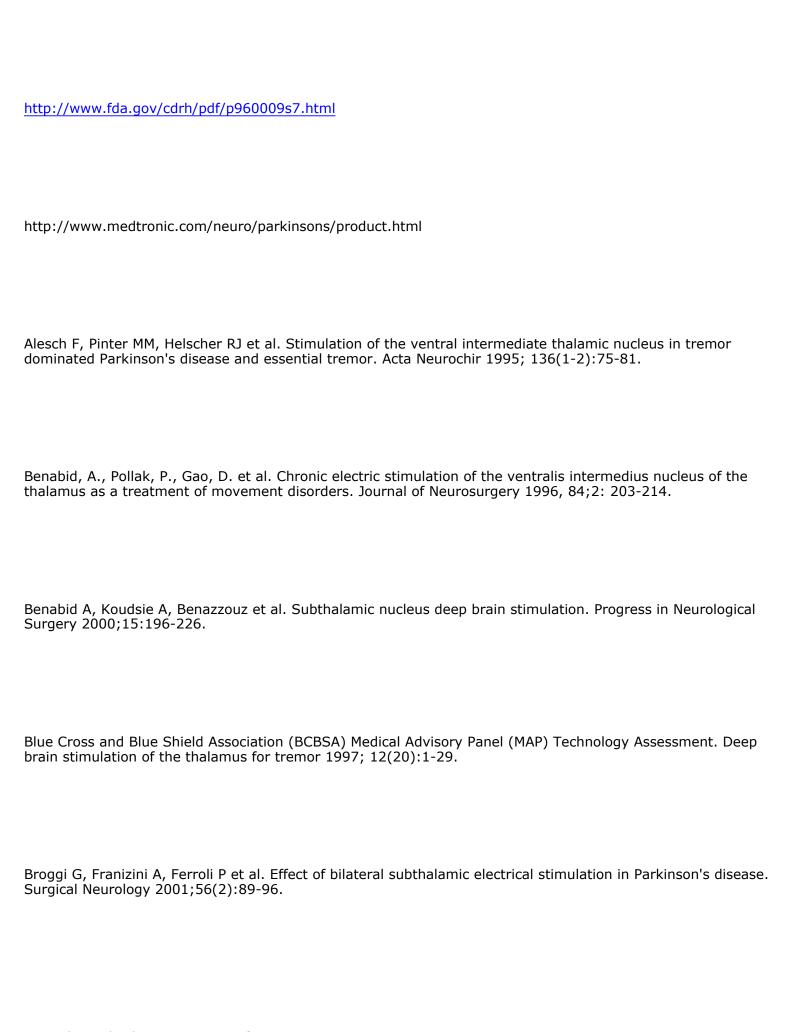
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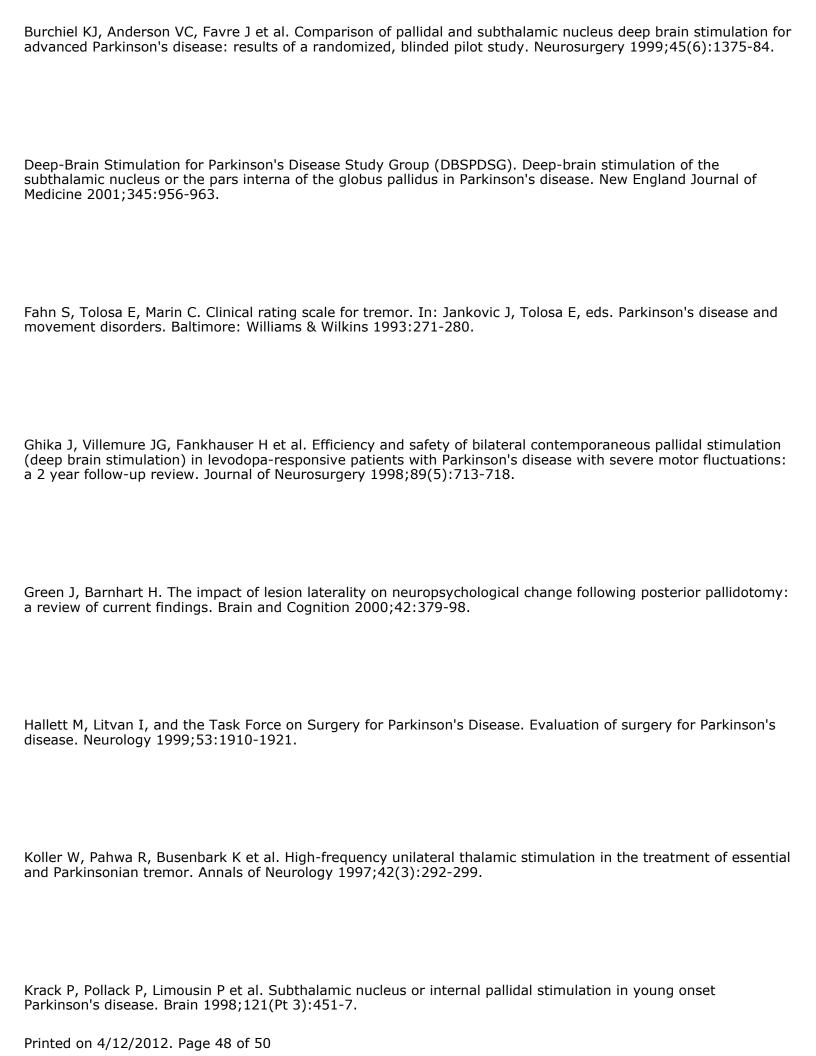
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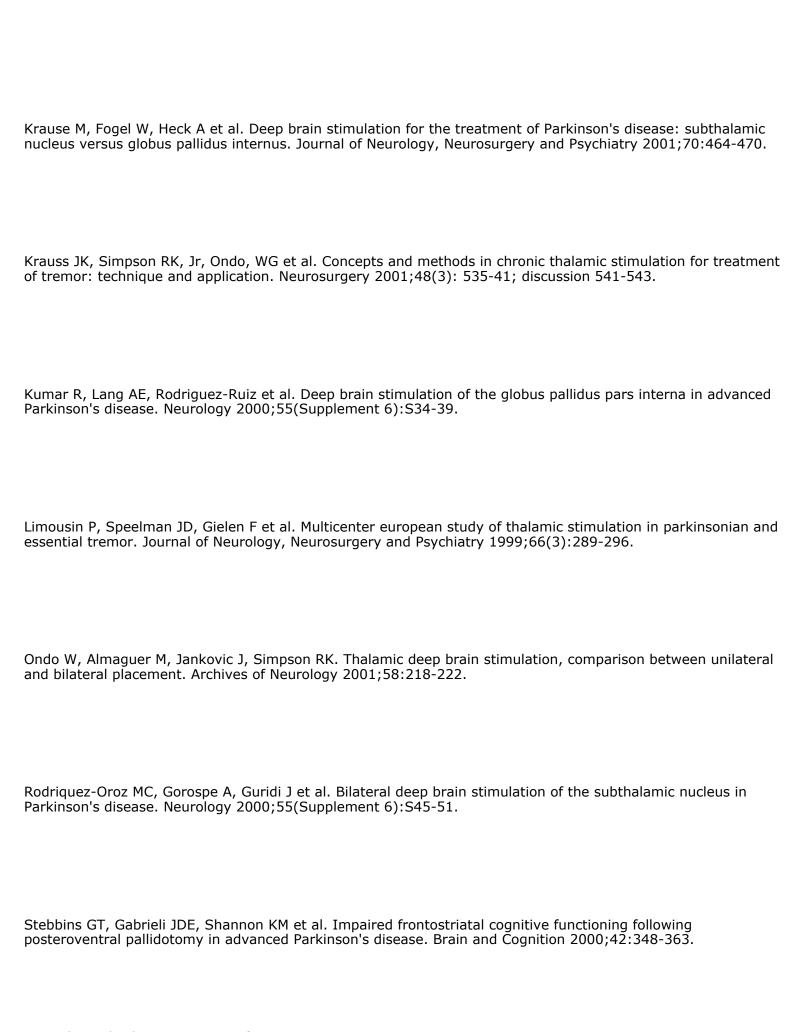
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